

Therapeutic Class Review
Topical: Testosterone

Overview/Summary¹⁻⁴

Testosterone is used for replacement therapy in the treatment of delayed male puberty and male hypogonadism (primary or hypogonadotropic). The injectable formulation, Delatestryl[®] (testosterone enanthate) has also been approved for use in female metastatic mammary cancer. Currently there are five different formulations of testosterone that are available in the United States; topical gel, subcutaneous implant, intramuscular injection, mucoadhesive buccal system and transdermal system. There is also a capsule formulation for oral administration available only in Canada.

The different testosterone formulations share common indications and produce similar effects on the body however there are several limitations associated with the different formulations. For example, intramuscular injections are painful and result in wide fluctuations in serum testosterone levels. Orally available testosterone is quickly metabolized by the liver and the topical preparations, in particular the transdermal system, are associated with application site reactions. The following review will include only the topical testosterone agents.

Androderm[®], AndroGel[®] Gel and Testim[®] Gel are FDA approved for testosterone replacement therapy in men for conditions associated with a deficiency or absence of endogenous testosterone which include primary or hypogonadotropic hypogonadism. Androderm[®] is a transdermal system while AndroGel[®] Gel and Testim[®] Gel are both topical gels. All topical testosterone agents are similar in efficacy and share the same safety concerns; however, Androderm[®] is associated with a higher incidence of application site reactions.

Hypogonadism refers to a defect of the reproductive system which results in a lack of function of the gonads (testes and ovaries). It can be categorized by the level of the reproductive system that is defective. Primary hypogonadism is hypogonadism resulting from a defect of the gonads. Secondary hypogonadism, also known as hypogonadotropic hypogonadism, results from defects in the hypothalamus or pituitary.

The human body has two principle gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are essential for reproduction. The gonads are the primary target organs for FSH and LH. Specifically in men, LH stimulates the synthesis and secretion of testosterone and FSH stimulates the production of sperm. The major regulator of the secretion of FSH and LH is gonadotropin-releasing hormone (GnRH). GnRH is released from the hypothalamus which stimulates the secretion of FSH and LH from the anterior pituitary. In a classic negative feedback loop, increased secretion of the sex steroids testosterone, estrogen and progesterone from the gonads, inhibits the continued secretion of GnRH.

In men, hypogonadism can lead to defective primary or secondary sexual development and infertility. The clinical manifestations that result depend on the age of onset of the condition. When hypogonadism develops before the age of puberty the manifestations include small testes, phallus and prostate, scant pubic and axillary hair, disproportionately long arms and legs, reduced male musculature, gynecomastia and a persistently high-pitched voice. Postpubertal hypogonadism results in slowly evolving and subtle clinical signs and symptoms that may include a progressive decrease in muscle mass, loss of libido, impotence, decreased semen volume and decreased ability to concentrate.

Medications¹⁻³

The topical testosterone agents included in the following review are listed in Table 1.

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Testosterone transdermal system (Androderm [®])	Androgen	-
Testosterone 1% gel (AndroGel [®] Gel)	Androgen	-
Testosterone 1% gel (Testim [®] Gel)	Androgen	-

Indications¹⁻³**Table 2. Food and Drug Administration Approved Indications**

Drug	Primary hypogonadism (congenital or acquired)	Hypogonadotropic hypogonadism (congenital or acquired)
Androderm [®]	✓	✓
AndroGel [®] Gel	✓	✓
Testim [®] Gel	✓	✓

In addition to the FDA approved indications, testosterone may be used off-label for conditions such as male infertility, osteoporosis in males, weight gain, androgen deficiency in men with AIDS wasting, cognitive function finding and gender identity disorder. Testosterone may also be used in combination with estrogen products in postmenopausal women with decreased sexual desire.

Pharmacokinetics¹⁻³**Table 3. Pharmacokinetics**

Drug	Bioavailability (%)	Absorption (%)	Renal Excretion (%) [*]	Active Metabolites [‡]	Serum Half-Life (hours)
Androderm [®]	10	10	90	Yes	1.2
AndroGel [®] Gel	10	10	90	Yes	0.12-1.7
Testim [®] Gel	10	10	90	Yes	0.12-1.7

^{*}Intramuscular testosterone administration

[‡]Estradiol and Dihydrotestosterone

Clinical Trials⁵⁻⁹

In a randomized, multi-dose, multi-center, active-controlled study comparing two doses of Testim[®] Gel and a transdermal testosterone system, 100 mg of Testim[®] Gel produced significantly higher serum levels of testosterone (T), free T and dihydrotestosterone (DHT) ($P < 0.05$, < 0.001).⁵ All three treatments produced significant increases in lean body mass (LBM) ($P < 0.001$, < 0.05 , < 0.05) while only Testim[®] 100 mg produced significant decreases in percentage of fat ($P < 0.05$). Significant differences between treatment groups were seen for the alleviation of negative mood ($P < 0.05$) and improvements in spontaneous erections ($P < 0.05$) favoring Testim[®] over transdermal testosterone. However, all three treatment groups produced significant improvements in sexual motivation, sexual desire and sexual performance ($P < 0.05$ for all measures). The transdermal testosterone system was associated with more treatment-emergent adverse events.

In a second study comparing two doses of Testim[®], Androderm[®] and placebo, all treatment groups produced similar increases in serum T and DHT levels.⁶ All treatment groups produced increases in LBM, however increases with Testim[®] 100 mg achieved significance over Androderm[®] and placebo ($P < 0.05$ for each measure). Both Testim[®] and Androderm[®] resulted in significant decreases in fat mass (FM) compared to placebo ($P < 0.01$). Only Testim[®] 100 mg produced significant improvements in sexual

function over placebo ($P < 0.001$). There were no significant differences among treatment groups in improving mood and Androderm[®] was associated with more treatment-emergent adverse events.

In comparing two doses of AndroGel[®] to Androderm[®], Swerdloff et al found that AndroGel[®] 100 mg produced significantly higher levels of T ($P = 0.001$) and free T ($P = 0.001$) compared to AndroGel[®] 50 mg and Androderm[®].⁷ Increases in serum DHT levels were significant with both doses of AndroGel[®] compared to Androderm[®] ($P = 0.001$). The discontinuation rate, mostly due to adverse skin reactions, was significantly greater in the Androderm[®] group ($P = 0.0002$).

Wang et al compared two doses of AndroGel[®] and Androderm[®] and showed that average serum T levels increased greatest with AndroGel[®] 100 mg (P values not reported).⁸ A decrease in percent body fat and total fat mass occurred in all treatment groups however was only significant for AndroGel[®]. All treatment groups produced significant improvements in sexual function ($P = 0.0001$ for all measures). Treatment with AndroGel[®] resulted in significant increases in prostate specific antigen levels ($P = 0.008, 0.05$). Skin irritation at the application site occurred in 65.8%, 5.3% and 5.7% of patients in the Androderm[®], AndroGel[®] 100 mg and 50 mg groups. This study also showed that all treatment groups caused a significant increase in hemoglobin (Hgb) and hematocrit (Hct) but had no overall effects on lipid profiles or blood chemistries.

In an extension study, three doses of AndroGel[®] were observed for a period of 36 months.⁹ Long-term treatment with AndroGel[®] maintained increased levels of serum T and improvements in sexual function, positive mood and body composition. A gradual significant improvement in hip and spine bone mineral density was also observed ($P = 0.0004, 0.0001$). Increases in Hgb and Hct plateaued at 12 months and clinically insignificant increases in high-density lipoprotein cholesterol (HDL-C), serum creatinine (Cr) and total bilirubin were seen. Serum levels of prostate specific antigen showed no further significant increases past 6 months of treatment. Treatment emergent adverse events included application site reactions (7.4%) and acne (7.4%) and gynecomastia developed in 8 more patients.

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>McNicholas et al⁵</p> <p>Testim Gel 50 mg DAILY in the morning</p> <p>vs.</p> <p>Testim Gel 100 mg DAILY in the morning</p> <p>vs.</p> <p>Andropatch* patch 2.5 mg two patches DAILY in the morning</p>	<p>R, MD, MC, AC, DB, OL</p> <p>Hypogonadal men, 31-80 years old, morning serum T level ≤ 10.4 nmol/L at screening with one or more symptoms of low T</p>	<p>N=208</p> <p>90 days</p>	<p>Primary: 24-hour PK profiles at days 30, 60 and 90 days</p> <p>Treatment effectiveness measured by body composition and mood and sexual function data at 30, 60 and 90 days</p> <p>Incidence of treatment-emergent adverse events</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>At 90 days, mean increases in serum T levels was significant for Testim 100 mg (12.41 nmol/l) over Testim 50 mg (6.54 nmol/L, $P<0.05$) and Andropatch (3.82 nmol/L, $P<0.001$). Results at 30 and 60 days were consistent with those at 90 days. The same results were also seen with the mean increase from baseline in free T levels.</p> <p>At 90 days, mean increases in DHT levels with Testim 100 mg was significant over Testim 50 mg ($P<0.05$) and Andropatch ($P<0.001$). Testim 50 mg was also significant over Andropatch at 90 days ($P<0.001$). Results at 30 and 60 days were consistent with those at 90 days.</p> <p>Significant within-treatment group changes in LBM were seen for all three treatment groups; 0.9 kg ($P<0.05$), 1.5 kg ($P<0.001$) and 1.0 kg ($P<0.05$) for Testim 50 mg and 100 mg and Andropatch. Significant within-treatment group mean changes in percentage fat were only seen with Testim 100 mg; -0.7 ($P<0.05$). There were no statistically significant changes in BMD within any of the three treatment groups.</p> <p>No significant differences in improvement in positive mood were seen among the three treatment groups. There were significant differences between treatment groups at 90 days for the alleviation of negative mood favoring Testim over Andropatch ($P<0.05$).</p> <p>At 90 days there were significant within-treatment group improvements from baseline in all three groups in sexual motivation, sexual desire and sexual performance ($P<0.05$). Both Testim groups had a statistically significant within-treatment improvement in spontaneous erections at all times from baseline ($P<0.05$). Andropatch produced no significant improvement in spontaneous erections at any time.</p> <p>The incidence of treatment-emergent adverse events was 35% for the Testim 50 mg, 29% for the Testim 100 mg and 63% for the Andropatch groups. Most commonly reported adverse events were erythema, irritation and reactions at the application site.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Steidle et al ⁶ Testim Gel 50 mg DAILY in the morning vs. Testim Gel 100 mg DAILY in the morning vs. Androderm patch 2.5 mg 2 patches DAILY in the morning vs. Placebo	R, DB, OL, MD, MC, AC, PC Hypogonadal men, 20-80 years old, morning serum T level ≤ 10.4 nmol/L at screening with one or more symptoms of low T	N=406 90 days	Primary: Periodic 24-hour PK profiles Effect of normalizing serum T on body composition, sexual function, mood and BMD Safety Laboratory analysis Secondary: Not reported	Primary: At 30 days, all treatment groups had increased mean serum T and DHT concentrations. Testim 100 mg had a significant increase in mean changes in T concentrations over Androderm ($P<0.001$). Testim 50 mg and 100 mg had significant increases in mean changes in DHT concentrations over Androderm ($P<0.001$ for each comparison). By 90 days similar results were seen across treatment groups. At 90 days, mean change in LBM was 1.5 ± 4.5 , 1.7 ± 2.6 , 0.9 ± 1.8 and 0.6 ± 1.8 kg for Testim 50 mg and 100 mg, Androderm and placebo groups. Testim 100 mg was significant over Androderm and placebo ($P<0.05$ for each comparison). With the exception of placebo treatment, all treatments resulted in a decrease in FM, which were significant, compared with placebo ($P<0.01$). At 90 days, when compared to placebo, Testim 100 mg had significant improvements in spontaneous erections ($P<0.001$), sexual motivation ($P<0.05$), sexual desire ($P<0.01$) and sexual performance ($P<0.05$). No other treatment groups had significant improvements compared to placebo. All treatments resulted in mean improvements from baseline in both positive and negative mood scores with no significant differences among the treatment groups. The incidence of treatment-related adverse events was 29.1%, 36.9%, 62.7% and 40.4% for Testim 50 mg and 100mg, Androderm and placebo. At 90 days clinically notable decreases in total-C, LDL-C and HDL-C were seen with Testim 100 mg (P value not reported). Increases in Hgb and Hct were the highest with Testim compared to Androderm and placebo. Increases in PSA values were highest in the Androderm group (6.6%).
Swerdlhoff et al ⁷ AndroGel 50 mg DAILY vs.	R, MC, PG, OL, DB Hypogonadal men, 19-68	N=227 180 days	Primary: Serum T and free T levels on days 0, 1, 30, 90 and 180 days	Primary: At 30 and 90 days, AndroGel 100 mg produced significantly higher C_{avg} T levels over AndroGel 50 mg and Androderm; 27.46 ± 1.12 nmol/L vs. 19.17 ± 1.06 and 14.46 ± 0.68 nmol/L ($P=0.0001$). At 180 days, serum T levels and PK parameters were similar to those on days 30 and 90 in those

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>AndroGel 100 mg DAILY</p> <p>vs.</p> <p>Androderm 2.5 mg 2 patches DAILY</p> <p>At 60 days, men with serum T levels < 10.4 nmol/L who were applying AndroGel 50 mg and men with serum T levels > 34.7 nmol/L who were applying AndroGel 100 mg were instructed to apply AndroGel 75 mg once daily for days 91 through 180.</p>	<p>years old, morning serum T level ≤ 10.4 nmol/L at screening</p>		<p>Incidence of adverse events</p> <p>Serum DHT, E₂, FSH, LH, SHBG levels on 0, 30, 60, 90, 120, 150 and 180 days</p> <p>Secondary: Not reported</p>	<p>patients who continued their initial randomized treatment. Patients who were switched to AndroGel 75 mg, at 180 days had a C_{avg} T level of 20.84 ± 1.76 nmol/L. This value fell between the 180 day C_{avg} T levels achieved with AndroGel 50 mg (19.24 ± 1.18) and AndroGel 100 mg (24.72 ± 1.05).</p> <p>PK parameters of serum free T levels on days 1, 30, 90 and 180 mirrored those of serum T levels. The free T levels in the AndroGel 100 mg group was 1.4- and 1.7-fold higher than the AndroGel 50 mg and Androderm groups ($P=0.001$).</p> <p>The discontinuation rate at 90 days for Androderm (27.6%) was significantly higher than AndroGel 50 and 100 mg (8.2%, 6.4%; $P=0.0002$). Most patients discontinued treatment due to adverse skin reactions.</p> <p>Throughout the 180 days, increases in serum DHT levels were significant with AndroGel 50 and 100 mg over Androderm ($P=0.0001$). Mean serum increases to stable levels of E₂ occurred in 9.2%, 30.9% and 45.5% of patients in the Androderm and the 50 and 100 mg AndroGel groups ($P=0.001$).</p> <p>Serum SHBG levels showed a small decrease in all three treatment groups ($P=0.0046$).</p> <p>The mean percent suppression of serum LH levels was the smallest with Androderm (30-40%), intermediate with AndroGel 50 mg (55-60%) and most marked with AndroGel 100 mg (80-85%; $P<0.01$). The suppression of serum FSH paralleled that of serum LH levels.</p>
<p>Wang et al⁸</p> <p>AndroGel 50 mg DAILY</p> <p>vs.</p> <p>AndroGel 100 mg DAILY</p> <p>vs.</p>	<p>R, MC, PG, OL, DB</p> <p>Hypogonadal men, 19-68 years old, morning serum T level ≤ 10.4 nmol/L at</p>	<p>N=227</p> <p>180 days</p>	<p>Primary: Mean change from baseline in serum T concentrations on 0, 90, 180 days</p> <p>Mean change</p>	<p>Primary:</p> <p>On day 90 the average serum T concentration with AndroGel 100 mg (27.46 ± 1.12 nmol/L) was 1.4-fold higher than AndroGel 50 mg (19.17 ± 1.06 nmol/L) and 1.9-fold higher than Androderm (14.46 ± 0.68 nmol/L) (P value not reported). On day 180 average serum T concentrations for the treatment groups were 24.72 ± 1.05 nmol/L, 19.24 ± 1.18 nmol/L and 14.14 ± 0.88 nmol/L.</p> <p>The percent body fat and FM decreased in all treatment groups but was</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Androderm 2.5 mg 2 patches DAILY</p> <p>At 90 days, dose adjustments were made in the AndroGel groups based on the pre-application serum T levels on day 60. Twenty subjects in the AndroGel 50 mg group had their dose increased to 75 mg of AndroGel and 20 subjects in the AndroGel 100 mg group had their dose reduced to 75 mg of AndroGel</p>	screening		<p>from baseline in body composition on 0, 90, 180 days</p> <p>Mean change from baseline in muscle strength on 0, 90, 180 days</p> <p>Mean change from baseline in sexual function and mood on 0, 30, 60, 90, 120, 150, 180 days</p> <p>Degree of skin irritation</p> <p>Mean change from baseline in serum PSA levels on 0, 30, 90 days</p> <p>Mean change from baseline in Hgb, Hct, lipid profiles and blood chemistries</p> <p>Secondary: Non Reported</p>	<p>only significant with AndroGel. At 90 days the total FM was significantly decreased with AndroGel 50 mg and 100 mg ($P=0.0065$, 0.0001). At 180 days the total FM decreased further with AndroGel 100 mg ($P=0.008$). At 90 days, the percent body fat was significantly decreased with AndroGel ($P=0.0018$, 0.001) and remained significant at 180 days.</p> <p>Similarly significant increases in arm and leg muscle strength was seen in all three treatment groups without intergroup differences on days 90 and 180 (P values ranges between 0.0001-0.08).</p> <p>All subjects, despite treatment group, show significant improvement in sexual motivation ($P=0.0001$), sexual desire ($P=0.0001$), sexual performance ($P=0.0001$), self-assessment of satisfaction of erection ($P=0.0001$) and percentage of full erection ($P=0.0001$). All three treatment groups showed significant improvement in positive mood scores ($P=0.0001$) and a decrease in negative mood scores ($P=0.0001$) without significant between-group differences.</p> <p>Minimal skin irritation at the application site was seen in 5.7% and 5.3% of patients in the AndroGel 50 mg and 100 mg group. Minimal to severe skin irritation occurred in 65.8% of patients in the Androderm group.</p> <p>Mean serum PSA levels significantly increased with AndroGel 100 mg ($P=0.008$) and 50 mg ($P=0.05$) with no significant increase in the Androderm group.</p> <p>As a group, both Hgb and Hct increased ($P=0.0001$) with statistical significance across treatment groups ($P=0.0001$). There were no overall treatment effects or intergroup differences in serum concentrations of total, HDL and LDL cholesterol or TG (data not provided).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Wang et al⁹</p> <p>AndroGel 50 mg DAILY</p> <p>vs.</p> <p>AndroGel 75 mg DAILY</p> <p>vs.</p> <p>AndroGel 100 mg DAILY</p>	<p>R, MC, PG, OL, EX</p> <p>Hypogonadal men, 19-68 years old, single morning serum T level at screening of ≤ 10.4 nmol/L</p>	<p>N=163</p> <p>36 months</p>	<p>Primary:</p> <p>Mean changes from baseline in serum T, free T, DHT, E₂, SHBG, LH and FSH</p> <p>Mean changes from baseline in sexual function and mood</p> <p>Mean changes from baseline in body composition</p> <p>Mean changes from baseline in bone turnover markers</p> <p>Mean changes from baseline in muscle strength and BMD</p> <p>Mean change from baseline in Hgb, Hct, lipid profiles and blood chemistries</p> <p>Mean changes from baseline in</p>	<p>Primary:</p> <p>Mean serum T levels were significantly different ($P=0.012$) between dosing groups at baseline (6 months of TRT). At 12 months, differences among the dosing groups became smaller but remained significant ($P=0.042$). Serum free T levels followed the same pattern as T.</p> <p>Mean serum DHT levels were different in the three dosing groups at 12 ($P=0.0031$) and 24 ($P=0.018$) months with the highest levels seen with AndroGel 100 mg. Mean serum E₂ levels progressively increased from 6 to 24 months ($P=0.0001$) with significant differences between treatment groups. The highest levels of serum E₂ was seen with AndroGel 100 mg. No significant change in SHBG was seen. Suppression of LH and FSH was maintained throughout with no significant changes after 6 months. The suppression was more pronounced with AndroGel 100 mg.</p> <p>Significant improvements in sexual desire, enjoyment with or without a partner, percent full erection, self-assessment of satisfaction with erections were maintained as a group throughout the study period.</p> <p>Positive mood scores were improved with treatment and were sustained ($P=0.0022$). Negative mood parameters were decreased and remained significantly lower ($P=0.0013$) than baseline without further changes after 6 months.</p> <p>Average total body mass increased by 1.2 ± 0.3 kg at 6 months ($P=0.0157$) and did not significantly change with continued therapy. LBM increased significantly ($P=0.0001$) from baseline and remained increased throughout the study. A significant decrease in FM was seen at 30 months ($P=0.088$) without significant differences between doses.</p> <p>Serum PTH levels significantly increased from baseline ($P=0.0001$) and continued to increase from 6 ($P=0.0002$) until 12 months when it remained stable throughout the rest of the treatment period. Serum SALP levels followed the same pattern ($P=0.001$). At 12 months serum osteocalcin was significantly elevated and remained elevated throughout treatment ($P=0.0001$). Serum procollagen levels transiently increased then steadily</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			<p>serum PSA and prostate disease</p> <p>Incidence of adverse reactions</p>	<p>increased from 6 months to reach significant levels by 36 months ($P=0.0001$).</p> <p>Muscle strength increased but did not reach significance over time due to the large variation in patients.</p> <p>BMD of the hip ($P=0.0004$) and spine ($P=0.0001$) showed a gradual and progressive increase with treatment. No significant differences among treatment doses or older and younger patients were observed.</p> <p>Serum Hgb and Hct concentrations increased, compared with month 0 ($P=0.0001$) and month 6 ($P=0.001$) and plateaued at 12 months.</p> <p>Small statistically significant increases in serum HDL-C levels ($P<0.001$), Cr ($P<0.001$) and total bilirubin ($P=0.001$) were seen but were not clinically significant. No significant changes in total-C, LDL-C, serum liver enzymes or other clinical chemistry parameters were observed.</p> <p>The mean serum PSA was 1.11 ± 0.08 at 6 months and showed no further significant increases with continued treatment.</p> <p>Application-site reactions occurred in 12 of the 163 (7.4%) patients. Acne occurred in 12 (7.4%) of patients and gynecomastia was observed in 8 more patients.</p>

*Agent not available in the United States

AC=active-controlled, DB=double-blind, ES=extension study, MC=multicenter, MD=multi-dose, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
 BMD=bone mineral density, C=cholesterol, C_{avg} =average concentration, Cr=creatinine, DHT=dehydroepiandrosterone, E_2 =Estradiol, FM=fat mass, FSH=follicle-stimulating hormone, Hct=hematocrit,
 HDL=high density lipoprotein, Hgb=hemoglobin, LBM=lean body mass, LH=luteinizing hormone, PK=pharmacokinetics, PSA=prostate specific antigen, PTH=parathyroid hormone, SALP=bone-specific alkaline phosphatase, SHBG=sex hormone-binding globulin, T=testosterone, TG=triglycerides, TRT=testosterone replacement therapy

Special Populations¹⁻³**Table 5. Special Populations**

Drug	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Androderm [®]	No observed differences based on age. Not studied in patients < 15 years of age	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	X	Do not use in women.
AndroGel [®] Gel	No observed differences based on age. Not studied in the pediatric population.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	X	Must not be used in women.
Testim [®] Gel	No observed differences based on age. Not studied in patients < 18 years of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	X	Must not be used in nursing mothers.

Adverse Drug Events¹⁻³**Table 6. Adverse Drug Events**

Adverse Event	Brand Name	Reported Frequency (%)
Application site reactions	Androderm [®]	56*
	AndroGel [®] Gel	3-5
	Testim [®] Gel	2-4
Acne	Androderm [®]	Not reported
	AndroGel [®] Gel	1-8
	Testim [®] Gel	<1
Burn-like blister reaction under system	Androderm [®]	12
	AndroGel [®] Gel	Not reported
	Testim [®] Gel	Not reported
Decreased libido	Androderm [®]	<1
	AndroGel [®] Gel	1-3
	Testim [®] Gel	Not reported
Depression	Androderm [®]	3
	AndroGel [®] Gel	1
	Testim [®] Gel	Not reported
Gynecomastia	Androderm [®]	Not reported
	AndroGel [®] Gel	1
	Testim [®] Gel	1
Headache	Androderm [®]	4
	AndroGel [®] Gel	3-4
	Testim [®] Gel	1
Hypertension	Androderm [®]	<1
	AndroGel [®] Gel	3
	Testim [®] Gel	Not reported

Adverse Event	Brand Name	Reported Frequency (%)
Lab test abnormal [±]	Androderm [®]	Not reported
	AndroGel [®] Gel	3-6
	Testim [®] Gel	1-2
Prostate disorders	Androderm [®]	5
	AndroGel [®] Gel	3-5
	Testim [®] Gel	1

*Combined incidence of pruritus at application site, erythema at application site, vesicles at application site, burning at application site and induration at application site per the package insert.

±Lab tests include elevated hemoglobin or hematocrit, hyperlipidemia, elevated triglycerides, hypokalemia, decreased high-density lipoprotein, elevated glucose, elevated creatinine and elevated total bilirubin.

Contraindications / Precautions¹⁻³

Topical testosterone is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate. In addition, none of the topical testosterone products are indicated for use in women. Due to the potential harm testosterone may cause to the fetus, pregnant women should avoid skin contact with the testosterone application sites in men.

Geriatric patients who are treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma with the use of topical testosterone. Geriatric patients and others with clinical or demographic characteristics associated with an increased risk of prostate cancer should be evaluated for the presence of prostate cancer prior to initiation of testosterone replacement therapy (TRT). If TRT is initiated in these patients, appropriate monitoring for prostate cancer is recommended. Edema with or without congestive heart failure may be a serious complication of TRT in patients with preexisting cardiac, renal or hepatic disease. The development of gynecomastia and sleep apnea are also warnings associated with TRT.

While using a topical testosterone agent there is a potential to transfer testosterone to another person if vigorous skin-to-skin contact with the application site occurs. Patients should be instructed to wash their hands immediately with soap and water after applying any of the topical testosterone agents. To prevent transfer to another person, patients who apply AndroGel[®] Gel or Testim[®] Gel should cover the application site with clothing after the gel has dried. If contact is made with another individual they should be washed with soap and water as soon as possible.

Drug Interactions¹⁻³

Table 7. Drug Interactions

Drug	Interacting Medication or Disease	Potential Result
Drug class (all)	Oxyphenbutazone	Concurrent administration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone.
Drug class (all)	Insulin	In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements.
Drug class (AndroGel [®] , Testim [®])	Corticosteroids	The concurrent administration of testosterone with ACTH or corticosteroids may enhance edema formation.
Drug class (Androderm [®])	Anticoagulants	The concurrent administration of testosterone with oral anticoagulants

Drug	Interacting Medication or Disease	Potential Result
		leads to a decrease in anticoagulant requirements and, therefore, increases the risk of bleeding.

Dosage and Administration¹⁻³**Table 8. Dosing and Administration**

Drug	Adult Dose	Pediatric Dose	Application Site	Availability
Androderm [®]	<u>Primary hypogonadism:</u> Transdermal system: initial; 5 mg applied once nightly, maintenance; 2.5-7.5 mg/day <u>Hypogonadotropic hypogonadism:</u> Transdermal system: initial; 5 mg applied once nightly, maintenance; 2.5-7.5 mg/day	Safety and efficacy in children have not been established	Back, abdomen, upper arms and thighs	Transdermal system: 2.5mg 5 mg
AndroGel [®] Gel [†]	<u>Primary hypogonadism:</u> Gel: initial; 5 gm applied once daily in the morning, maintenance; 5-10 gm/day, maximum; 10 gm/day <u>Hypogonadotropic hypogonadism:</u> Gel: initial; 5 gm applied once daily in the morning, maintenance; 5-10 gm/day, maximum; 10 gm/day	Safety and efficacy in children have not been established	Shoulders, upper arms and abdomen	Non-aerosol, metered dose pumps: 1.25 mg Unit-dose aluminum foil packets: 2.5 gm 5 gm
Testim [®] Gel [†]	<u>Primary hypogonadism:</u> Gel: initial; 5 gm applied once daily in the morning, maintenance; 5-10 gm/day, maximum; 10 gm/day <u>Hypogonadotropic hypogonadism:</u> Gel: initial; 5 gm applied once daily in the morning, maintenance; 5-10 gm/day, maximum; 10 gm/day	Safety and efficacy in children have not been established	Shoulders and upper arms	Unit-dose tubes: 5 gm

[†] Application of 5 gm delivers 50 mg of testosterone with 5 mg systemically absorbed. Application of 10 gm delivers 100 mg of testosterone with 10 mg systemically absorbed.

Androderm[®] transdermal systems should be applied to a clean, dry, intact area of skin on the back, abdomen, upper arms or thighs. Application sites should rotate, with an interval of seven days between applications to the same site. Application on bony prominences or any part of the body subject to prolonged pressure during sleep or sitting should be avoided. In addition, Androderm[®] should not be

applied to the scrotum. The use of hydrocortisone cream, applied after the transdermal system has been removed, may ameliorate mild skin irritations that may develop with the use of Androderm®.

AndroGel® Gel can be applied to a clean, dry area of skin on the shoulders, upper arms or abdomen. The multi-dose AndroGel® Pump must be primed before using it for the first time. After priming, to achieve the daily prescribed dose, each actuation will deliver 1.25 gm of product. Testim® Gel may be applied to either the shoulders or upper arms. The gels should be allowed to dry before dressing. AndroGel® Gel and Testim® Gel should not be applied to genitals or to skin with open sores, wounds or irritation.

Hands should be washed immediately after application of any of the topical testosterone products.

Drug Acquisition Cost

Table 9. Drug Acquisition Cost

Medication	Dosage Form	Strengths	Availability	Cost Per Unit*
Androderm®	Transdermal system	-	2.5 mg	\$4.24/patch
			5 mg	\$8.48/patch
AndroGel® Gel†	Gel	1%	2.5 gm	\$8.28/package
			5 gm	\$8.75/package
AndroGel® Gel Pump [‡]	Gel	1%	1.25 gm	\$131.25/bottle (\$2.19/actuation)
Testim® Gel†	Gel	1%	5 gm	\$8.90/tube

*AWP as of 11/5/2008

[‡]Sixty actuations per 75 gm bottle, 1.25gm/actuation

† Application of 5 gm delivers 50 mg of testosterone with 5 mg systemically absorbed

Potential Advantages

- Topical testosterone agents produce more consistent delivery of testosterone into the systemic circulation compared to the other formulations of testosterone.
- AndroGel® Gel and Testim® Gel are associated with less application-site reactions than with Androderm®.

Potential Disadvantages/Unanswered Questions

- Administration difficulties.
- Potential for off-label use.

Clinical Guidelines

According to the current clinical guidelines testosterone replacement therapy (TRT) may be used in symptomatic hypogonadal men with low serum testosterone levels (T). In addition, the American Association of Clinical Endocrinologists (AACE), recommend that TRT maintain T levels within physiologic range.⁴ The European Association of Urology (EAU) recognize that a treatment period of between 3 to 6 months is required to see clinical benefits from TRT, however any improvements in bone mineral density require a longer treatment period.¹²

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
The Endocrine Society of Australia: Consensus Guidelines for Androgen Prescribing (2000) ¹⁰	<ul style="list-style-type: none"> • Androgen replacement therapy (ART) is usually life-long, and should only be started after androgen deficiency has been proven by hormone assays. The therapeutic goal of ART is to maintain physiological levels of testosterone (T). • Choice of modality for ART depends on convenience, cost, availability and familiarity.¹¹

Clinical Guideline	Recommendations
The American Association of Clinical Endocrinologists (AACE): Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients (2002) ⁴	<ul style="list-style-type: none"> • Testosterone replacement therapy (TRT) should maintain testosterone (T) levels within the physiologic range (280 and 800 ng/dl). • TRT can be used in men with hypogonadism who are not interested in fertility or who are not able to achieve fertility. • Treatment of men with hypogonadism with T results in increased sexual interest and increased number of spontaneous erections. • Secondary sex characteristics such as increased muscle mass, beard growth, growth of pubic and axillary hair, and phallus growth improve with T therapy. • In prepubertal-onset hypogonadotropic hypogonadism, diminished bone mass may be only marginally improved by TRT. • No specific recommendations can be made on the possible normalization of growth hormone levels in elderly men with TRT. Further research is needed to clarify the potential risks and benefits associated with therapy. • Whether TRT in men with hypogonadism increases, decreases or has a neutral effect on cardiovascular risk remains uncertain.
The Endocrine Society: Clinical Practice Guideline Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes (2006) ¹¹	<ul style="list-style-type: none"> • Testosterone replacement therapy (TRT) is recommended for symptomatic men with classical androgen deficiency syndromes who have low testosterone (T) levels to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density. • TRT is suggested in men with low T levels and low libido to improve libido and to men with erectile dysfunction (ED) who have unequivocally low T levels, after evaluation of underlying causes of ED and consideration of established therapies for ED. • TRT should not be offered to all older men with low T levels. Clinicians should offer TRT on an individualized basis to older men with consistently low T levels on more than one occasion and significant symptoms of androgen deficiency. • Short-term testosterone therapy may be considered as adjunctive therapy in HIV-infected men with low T levels and weight loss to promote weight maintenance and gains in lean body mass and muscle strength. • Short-term testosterone therapy may be offered to men receiving high dose glucocorticoids who have low T levels to promote preservation of lean body mass and bone mineral density.
European Association of Urology: Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA and ASA Recommendations (2008) ¹²	<ul style="list-style-type: none"> • Data indicates testosterone (T) levels progressively fall with age and that significant percentage of men over 60 years old have serum T levels below the lower limits of young adult men. • A period of 3-6 months of testosterone replacement treatment (TRT) is adequate to see an improvement in libido and sexual function, muscle function and improved body fat. If the clinical benefits are not observed within this time period, TRT should be discontinued and further investigation for other causes of symptoms is then mandatory. • Improvements in bone mineral density require a longer treatment period. • All of the currently available T agents, intramuscular, subdermal, transdermal, oral and buccal preparations, are safe and effective. Pharmacokinetic parameters and other agent-specific limitations should be considered when choosing therapy.

⁴At the time this article was published the testosterone modalities currently available were testosterone injections, implants, or capsules

Conclusions

Hypogonadism refers to a defect in the male reproductive system which leads to defective primary or secondary sexual development and infertility. It is characterized by low serum testosterone (T) levels and is associated with impotence and decreased sexual desire, fatigue and loss of energy, depression, regression of secondary sexual characteristics and osteoporosis.

According to the clinical guidelines regarding testosterone replacement therapy (TRT), all of the currently available testosterone formulations are similar in efficacy and produce the same clinical effects. The decision of which formulation to use for TRT depends on agent-specific limitations, patient preference, availability and cost. Specific to the topical formulations, several clinical studies have shown that Androderm[®], AndroGel[®] Gel and Testim[®] Gel all restore serum testosterone concentrations to within normal limits and maintain sexual characteristics, sexual behavior, mood, muscle development and improve bone mineral density in hypogonadal men. In three head-to-head trials, results favored the use of Testim[®] Gel and AndroGel[®] Gel over the transdermal system Androderm[®].^{6,7,8} Significantly higher serum levels of T and dihydrotestosterone were achieved with AndroGel[®] Gel or Testim[®] Gel therapy over Androderm[®]. In addition, the incidence of treatment-emergent adverse events was higher in the Androderm[®] treatment groups.

Currently, none of the clinical guidelines differentiate between the different topical testosterone agents. Androderm[®], AndroGel[®] Gel and Testim[®] Gel are all indicated for the treatment of primary and hypogonadotropic hypogonadism. Androderm[®] is a transdermal system while AndroGel[®] Gel and Testim[®] Gel are both topical gels. All of the topical testosterone agents are administered once daily.

Appendix I: Other Insurance Coverage

Managed Care Organization	Current Coverage	Notes
MassHealth (Massachusetts Medicaid)	Covered	All topical testosterone agents are covered
New Hampshire Medicaid	No information	-
New York Medicaid	No information	-
MVP Healthcare	Tier 2 and Tier 3	Tier 2: AndroGel [®] Gel Pump 1%, AndroGel [®] Gel 1% and Testim [®] Gel 1% Tier 3: Androderm [®]
Cigna Healthcare	Tier 2	All topical testosterone agents are preferred branded products
Blue Cross Blue Shield of Vermont	Tier 3	Topical testosterone agents are not listed on the preferred brand list

Appendix II: Current Preferred Drug List (PDL) Alternatives

Medication	Cost/unit*	Dosing Frequency	Cost/30 days
Androderm [®] , 2.5, 5 mg (testosterone)	\$4.24/2.5 gm \$8.48/5 gm	2.5 - 7.5 mg once daily	\$127.20 - \$381.60
AndroGel [®] Gel [†] , 2.5, 5 gm (testosterone 1% gel)	\$8.28/2.5 gm \$8.75/5 gm	5 - 10 gm once daily	\$262.50 - \$525.00 (4 x 2.5 gm = \$993.00)
AndroGel [®] Gel Pump [‡] , 1.25 gm (testosterone 1% gel)	\$2.19/actuation (1.25 gm)	5 - 10 gm once daily	\$262.50 - \$525.00
Testim [®] Gel [†] , 5 gm (testosterone 1% gel)	\$8.90/5 gm	5 - 10 gm once daily	\$267.00 - \$534.00

*AWP as of 11/5/2008

[†] Application of 5 gm delivers 50 mg of testosterone with 5 mg systemically absorbed

[‡] Based on dosing per package insert, one AndroGel[®] Gel Pump bottle (75 gm testosterone, 60 actuations) will last 7.5 – 15 days.

References

1. Androderm® [package insert]. Corona (CA): Watson Pharma, Inc; 2005 Nov.
2. AndroGel® [package insert]. Marietta (GA): Unimed Pharmaceuticals, Inc; 2004 April.
3. Testim® [package insert]. Malvern (PA): Auxilium Pharmaceuticals, Inc; 2006 Feb.
4. Petak SM, Nankin HR, Spark RF, Swerdloff RS, Rodriguez-Rigau, LJ; American Association of Clinical Endocrinologists. Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients. *Endocrine Practice*. 2002 Dec;8(6):439-456.
5. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in Hypogonadal men, with improvements in body composition and sexual function. *BJU International*. 2003;91:69-74.
6. Steidle C, Schwartz S, Jacoby K, Sebree T, Smith T, Bachand et al. AA2500 Testosterone Gel Normalizes Androgen Levels in Aging Males with Improvements in Body Composition and Sexual Function. *J Clin Endocrinol Metab*. 2003;88:2673-2681.
7. Swerdloff RS, Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM et al. Long-term Pharmacokinetics of Transdermal Testosterone Gel in Hypogonadal Men. *J Clin Endocrinol Metab*. 2000;85:4500-4510.
8. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G et al. Transdermal Testosterone Gel Improves Sexual Function, Mood, Muscle Strength, and Body Composition Parameters in Hypogonadal Men. *J Clin Endocrinol Metab*. 2000;85:2839-2853.
9. Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ et al. Long-term Testosterone Gel (AndroGel) Treatment Maintains Beneficial Effects on Sexual Function and Mood, Lean and Fat Mass, and Bone Mineral Density in Hypogonadal Men. *J Clin Endocrinol Metab*. 2004;89:2085-2098.
10. Connway AJ, Handelsman DJ, Lording DW, Stuckey B, Zajac JD; Endocrine Society of Australia. Use, Misuse and Abuse of Androgens. The Endocrine Society of Australia Consensus Guidelines for Androgen Prescribing. *Med J Aust*. 2000;172(5):220-224.
11. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS et al; Endocrine Society. Clinical Practice Guideline: Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes. *J Clin Endocrinol Metab*. 2006;91:1995-2010.
12. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstorm WJ, Gooren LJ et al; European Association of Urology. Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations.